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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/216,604	12/17/98	GUO	Y

KM

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HM22/1108

EXAMINER	
DIBRINO,M	
ART UNIT	**PAPER NUMBER**
1644	8

DATE MAILED: 11/08/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/216,604	Guo, Y.
Examiner	**Group Art Unit**
Marianne DiBrino	1644

☒ Responsive to communication(s) filed on *Aug 29, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *5 and 12-16* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 5 and 12-16 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's amendment, filed 8/29/00 (Paper No. 7), is acknowledged and has been entered.

2. Applicant's election of the Invention of Group II (claims 5 and 12-16) and the species CD28: gp55 bispecific antibody as the bridge molecule and CD28 as the antigen in Paper No. 7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse.

The non-elected claims (1-4, 6-11 and 17-22) were canceled in the amendment filed 8/29/00.

Claims 5 and 12-16 are pending and are presently being examined.

The search of the prior art has been expanded to include bispecific mAb bridge molecules comprising gp115, gp95, gp210 and CD30. The elected species of bispecific mAb bridge molecule is anti-CD28:gp55.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Applicant is reminded of the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999; the following rejection is set forth herein.

Claims 5 and 12-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed immunogenic composition, or method of preparing a pharmaceutical composition, said composition comprising an isolated or

enriched antigen presenting cell (APC) which presents one or more antigens of patient's diseased cells in the MHC class I or class II complex of said APC and a bridge molecule capable of stimulating T cell activation comprising one or more binding sites for one or more costimulatory molecules on the surface of T cells, wherein said bridge molecule is attached to said APC.

The instant claims encompass a composition, and method of making said composition, comprising any APC and any bridge molecule capable of stimulating T cell activation comprising one or more binding sites for one or more costimulatory molecules on the surface of said T cells. There is insufficient disclosure in the specification on said composition and said method.

The specification discloses (on pages 6 and 7 at lines 29-31 and line 1, respectively) that said costimulatory T cell activation molecules include 4-1-BB, ICAM-1, ICAM-2, ICAM-3, LFA-1, LFA-2, VLA-1 VCAM-1, B7-1, B7-2 and other cell adhesion proteins and other cell surface proteins which can activate T cell costimulatory pathways through T cell surface proteins. The specification also discloses (on page 7 at lines 27-31 and continuing onto page 8 at lines 1-15) that costimulatory molecules on effector cells may be antigens, fatty acids, lipids, steroid and sugars that can stimulate or costimulate the effector cells' functions to destroy target cells, or may be one of the multitude of CD molecules listed on pages 7 and 8. The specification further discloses (on page 7 at lines 12-16) that bridge molecules include, but are not limited to, bispecific monoclonal antibodies, fusion proteins, organic polymers and hybrids of chemical and biochemical materials. The specification discloses bispecific antibodies CD28:gp55, CD28:gp95 CD28:gp115 and CD28:gp210 (figures and examples). The specification further discloses CD28:gp55, CD28:gp95, and CD28:gp210 armed HEPA 1-6 (hepatoma tumor cells), CD28:gp55 armed EL-4 (lymphoma cells) and CD28:gp55 armed SMCC-1 (colon carcinoma cells) (examples). The specification also discloses EL-4 or SMCC tumor cell armed -Bi-Mab anti-gp115:anti-4-1BB (4-1BB is a glycoprotein expressed on primed T CD4+ and CD8+ T cells) (Example 8). The specification also discloses primary and E1B deleted Adenovirus-infected liver cells armed with anti-gp115:anti-CD28 (Example 9). The specification discloses rat NTBII tumor cells or fused tumor cells (rat NTBII and mouse SMCC-1) armed with gp115:CD28 Bi-Mab (Example 11).

The specification discloses (on page 7 at lines 17-26) that the antigen on the target cell serving as an anchor for the bridge molecule can be any molecule, including but not limited to, proteins, glycoproteins, lipids, glycolipids, phospholipids, lipid aggregates, steroids, and carbohydrate groups such as disaccharides, oligosaccharides and polysaccharides, and further, may be transferrin receptor,

LDL receptor, gp55, gp95, gp115, gp210, CD44, ICAM-1, ICAM-2, collagen and fibronectin receptors, transferrin receptors, Fc receptor and cytokine receptors.

The specification discloses that the source of the diseased cells can include among others tumor cells (including unmodified tumor cells,, tumor cells modified with different approaches and primary culture), sources including liver cancer, hepatocellular carcinoma, lung cancer, gastric cancer, colorectal carcinoma, renal carcinoma, head and neck cancers, sarcoma, lymphoma, leukemia, brain tumors, osteosarcoma, bladder carcinoma, my[e]loma, melanoma, breast cancer, prostate cancer, ovarian cancer and pancreas carcinoma (page 8 at lines 18-27 and page 9 at line 1).

The specification discloses (on page 4 at lines 5-10) that the starting materials for the cellular vaccine can be a target diseased cell or an APC presenting one or more antigens associated with a disease such as dendritic cells, macrophages, B cells, and other cells fused with [a] diseased cell, pulsed antigens or transfected with antigen expressing nucleic acid.

The specification also discloses in vivo data on human hepatocellular carcinoma and human gastric cancer (Example 16).

The instant claims encompass bridge molecules that are not limited to bispecific monoclonal antibodies and tumor cells that are not limited to hepatocellular carcinoma cells, colon carcinoma cells and gastric cancer cells. There is insufficient disclosure in the specification on said composition and the components of said composition.

5. Claims 5 and 12-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method of preparing a composition and the said composition comprising CD28:gp55, CD28:gp95, and CD28:gp210 armed HEPA 1-6 (hepatoma tumor cells), CD28:gp55 armed EL-4 (lymphoma cells), CD28:gp55 armed SMCC-1 (colon carcinoma cells) (examples), EL-4 or SMCC tumor cell armed Bi-Mab anti-gp115:anti-4-1BB (4-1BB is a glycoprotein expressed on primed T CD4+ and CD8+ T cells) (Example 8), primary and E1B deleted Adenovirus-infected liver cells armed with anti-gp115:anti-CD28 (Example 9), or rat NTBII tumor cells or fused tumor cells (rat NTBII and mouse SMCC-1) armed with gp115:CD28 Bi-Mab (Example 11), does not reasonably provide enablement for a method of preparing a composition and the said composition comprising any antigen presenting cell which present antigens of any diseased cell armed with any bridge molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make or use the invention commensurate in scope with these claims.

The specification does not disclose how make and/or use the instant invention. The claimed method and composition encompasses a method of preparing a composition and the said composition comprising any antigen presenting cell which presents any antigen of any diseased cell armed with any bridge molecule. The specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass a method of preparing a composition and the said composition comprising any antigen presenting cell which presents any antigen of any diseased cell armed with any bridge molecule. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed compositions can be made and/or used.

The specification discloses (on pages 6 and 7 at lines 29-31 and line 1, respectively) that said costimulatory T cell activation molecules include 4-1-BB, ICAM-1, ICAM-2, ICAM-3, LFA-1, LFA-2, VLA-1 VCAM-1, B7-1, B7-2 and other cell adhesion proteins and other cell surface proteins which can activate T cell costimulatory pathways through T cell surface proteins. The specification also discloses (on page 7 at lines 27-31 and continuing onto page 8 at lines 1-15) that costimulatory molecules on effector cells may be antigens, fatty acids, lipids, steroid and sugars that can stimulate or costimulate the effector cells' functions to destroy target cells, or may be one of the multitude of CD molecules listed on pages 7 and 8. The specification further discloses (on page 7 at lines 12-16) that bridge molecules include, but are not limited to, bispecific monoclonal antibodies, fusion proteins, organic polymers and hybrids of chemical and biochemical materials. The specification discloses bispecific antibodies CD28:gp55, CD28:gp95 CD28:gp115 and CD28:gp210 (figures and examples). The specification further discloses CD28:gp55, CD28:gp95, and CD28:gp210 armed HEPA 1-6 (hepatoma tumor cells), CD28:gp55 armed EL-4 (lymphoma cells) and CD28:gp55 armed SMCC-1 (colon carcinoma cells) (examples). The specification also discloses EL-4 or SMCC tumor cell armed -Bi-Mab anti-gp115:anti-4-1BB (4-1BB is a glycoprotein expressed on primed T CD4+ and CD8+ T cells) (Example 8). The specification also discloses primary and E1B deleted Adenovirus-infected liver cells armed with anti-gp115:anti-CD28 (Example 9). The specification discloses rat NTBII tumor cells or fused tumor cells (rat NTBII and mouse SMCC-1) armed with gp115:CD28 Bi-Mab (Example 11).

The specification discloses (on page 7 at lines 17-26) that the antigen on the target cell serving as an anchor for the bridge molecule can be any molecule, including but not limited to, proteins, glycoproteins, lipids, glycolipids, phospholipids, lipid aggregates, steroids, and carbohydrate groups such as disaccharides,

oligosaccharides and polysaccharides, and further, may be transferrin receptor, LDL receptor, gp55, gp95, gp115, gp210, CD44, ICAM-1, ICAM-2, collagen and fibronectin receptors, transferrin receptors, Fc receptor and cytokine receptors.

The specification discloses that the source of the diseased cells can include among others tumor cells (including unmodified tumor cells,, tumor cells modified with different approaches and primary culture), sources including liver cancer, hepatocellular carcinoma, lung cancer, gastric cancer, colorectal carcinoma, renal carcinoma, head and neck cancers, sarcoma, lymphoma, leukemia, brain tumors, osteosarcoma, bladder carcinoma, my[e]loma, melanoma, breast cancer, prostate cancer, ovarian cancer and pancreas carcinoma (page 8 at lines 18-27 and page 9 at line 1).

The specification discloses (on page 4 at lines 5-10) that the starting materials for the cellular vaccine can be a target diseased cell or an APC presenting one or more antigens associated with a disease such as dendritic cells, macrophages, B cells, and other cells fused with [a] diseased cell, pulsed antigens or transfected with antigen expressing nucleic acid.

The specification also discloses in vivo data on human hepatocellular carcinoma and human gastric cancer (Example 16).

The instant claims encompass bridge molecules that are not limited to bispecific monoclonal antibodies and tumor cells that are not limited to hepatocellular carcinoma cells, colon carcinoma cells and gastric cancer cells. There is insufficient disclosure in the specification on said composition and the components of said composition.

The state of the art is unpredictable whether the claimed composition can be made and/or used because the bridge molecule can be any molecule (including a fusion protein, organic polymer and hybrid of chemical and biochemical materials) that is attached to said antigen presenting cell and the binding site(s) on the said bridge molecule can be a binding site for any costimulatory molecule (including an antigen, fatty acid, lipid, steroid, and sugar).

There is insufficient guidance in the specification as to how to practice the method of the instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

6. Claims 5 and 12-16 are drawn to a composition and method of preparing said composition, said composition comprising APC which present one or more antigens of said diseased cells in the MHC class I or MHC class II complex of said APC and further comprising and attached to said APC, a bridge molecule capable of stimulating T cell activation, said bridge molecule comprising one or more binding sites for one or more costimulatory molecules on the surface of T cells. Instant claims 13 is drawn to APC which are dendritic cells, macrophages or B cells, and instant claims 14-16 are drawn to one of: APC fused with a diseased cell from the patient mammal, an APC pulsed with peptide antigens of the diseased cells, or APC transfected with a nucleic acid capable of expressing one or more antigens of diseased cells or their precursors. With regard to application of prior art claims 5 and 12-16 are only entitled to priority of the instant application, i.e., 12/17/98, because the scope of the claimed invention is not disclosed in parent applications 60/019,639 and 08/872,527. The parent applications disclose compositions and methods of using said compositions, said compositions comprising an autologous diseased cell (as APC) attached to a bridge molecule, said autologous diseased cell being disclosed (in 08/872,527 on page 8 at lines 18-27 and continuing onto page 9 at lines 1-22) as a cell causing, propagating, aggravating or contributing to a disease in a patient mammal. The parent applications do not disclose the claimed method and composition comprising the APC of the instant application.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 5 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Guo et al (Nature Medicine, Volume 3(4), April 1997, pages 451-455).

Guo et al teach a method of preparation of a composition comprising hepa 1-6 tumor cells or EL-4 tumor cells (i.e., are diseased cells expressing tumor antigens) armed with one of three bispecific monoclonal antibodies: CD28:gp55, CD28:gp95 or CD28:gp210 (especially page 451, column 2, Abstract and page 452, column 1). Guo et al further teach that said composition induces protective immunity when administered to mice (especially page 452, column 1), i.e., is a pharmaceutical composition for stimulating T cell immune response. Guo et al teach that said tumor cells express very low levels of molecules necessary for antigen presentation and for adhesion (especially page 451, middle of column 2) and that cytokine treatment of said cells can enhance levels of said molecules (especially page 451

Abstract), i.e., the cells are low immunogenic diseased cells before cytokine treatment. It is an inherent property of the method of Guo et al that a pharmaceutically effective amount of the composition is collected because said composition induces protective immunity when administered to mice.

The reference teachings anticipate the claimed invention.

9. Claim 12 is rejected under 35 U.S.C. 102(b) as being anticipated by Shi et al (Proc. Amer. Assoc. Cancer Res. March 1996, Volume 37, page 480, Abstract No. 3278).

Shi et al teach an immunogenic composition comprising human liver tumor cells which possess tumor antigens and which have increased expression of Class I MHC molecules, ICAM-1 and B7 after induction with cytokines (i.e., the tumor cells are low immunogenic diseased cells before cytokine treatment and have the capacity to express tumor antigens at a higher level after cytokine treatment), and which are mixed with bispecific monoclonal antibody to CD28 and GP115X, a costimulatory molecule on T cells and a tumor antigen, respectively. Shi et al teach said composition is used to generate tumor-specific CTL in vitro, i.e., is immunogenic. The composition taught by Shi et al is present in tissue culture media (e.g., a pharmaceutically acceptable carrier). It is an inherent property of said human liver tumor cells to present one or more antigens of said liver tumor cells in the MHC Class I complex of said liver tumor cells since they are immunogenic for production of CTL which are restricted to Class I MHC.

The reference teachings anticipate the claimed invention.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 5 and 12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Shi et al (Proc. Amer. Assoc. Cancer Res. March 1996, Volume 37, page 480, Abstract No. 3278).

Shi et al teach an immunogenic composition comprising human liver tumor cells which possess tumor antigens and which have increased expression of Class I MHC molecules, ICAM-1 and B7, and which are mixed with bispecific monoclonal antibody to CD28 and GP115X, a costimulatory molecule on T cells and a tumor

antigen, respectively. Shi et al teach said composition is used to generate tumor-specific CTL, i.e., is immunogenic, and the human liver tumor cells function as antigen presenting cells). The composition taught by Shi et al is present in tissue culture media (e.g., a pharmaceutically acceptable carrier). It is expected that said human liver tumor cells present one or more antigens of said liver tumor cells in the MHC class I of said liver tumor cells since the tumor cells have increased levels of MHC class I and they are immunogenic for production of CTL. Shi et al further teach a method of using said composition to generate tumor specific CTLs as a strategy for human cancer immunotherapy.

Shi et al do not teach a method of preparing said composition wherein a pharmaceutically effective amount of the said liver tumor cells with the bispecific antibody attached is collected.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have collected an effective amount of said liver tumor cells with the bispecific antibody attached.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to quantitate the effects the said liver tumor cells with the bispecific antibody attached have or in order to effectively stimulate a discrete number of TILs or PBLs either in vitro, or to effectively stimulate said TIL or PBL cells present in a patient.

12. Claims 13-16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Shi et al (Proc. Amer. Assoc. Cancer Res. March 1996, Volume 37, page 480, Abstract No. 3278) as applied to claims 5 and 12 above, and further in view of Guo et al (Science, Volume 263, 1994, pages 518-520) and further in view of Van der Bruggen et al (WO 96/21673) and Hogan et al (J. Exp. Med., Volume 168, 1988, pages 725-736).

Shi et al teach an immunogenic composition comprising human liver tumor cells which possess tumor antigens and which have increased expression (through pretreatment with IFN-γ and TNF for 72 hours) of Class I MHC molecules, ICAM-1 and B7, and which are mixed with bispecific monoclonal antibody to CD28 and GP115X, a costimulatory molecule on T cells and a tumor antigen, respectively. Shi et al teach said composition is used to generate tumor-specific CTL (i.e., is immunogenic, and the human liver tumor cells function as antigen presenting cells). The composition taught by Shi et al is present in tissue culture media (i.e., a pharmaceutically acceptable carrier). It is expected that said human liver tumor cells present one or more antigens of said liver tumor cells in the MHC class I of

said liver tumor cells since the tumor cells have increased levels of MHC class I and they are immunogenic for production of CTL which are restricted by MHC class I. Shi et al further teach a method of using said composition to generate tumor specific CTL as a strategy for human cancer immunotherapy.

Shi et al do not teach said immunogenic composition, wherein the antigen presenting cell is a B cell, or wherein the antigen presenting cell is a B cell that is peptide pulsed with antigens of the tumor cells, or wherein the antigen presenting cell is fused with a diseased cell from a patient mammal.

Guo et al teach that activated B cells are the most effective antigen presenting cells (page 518, column 1, second paragraph). Guo et al further teach an antigen presenting cell that is a fusion of a tumor cell with an activated B cell (page 518, column 1, second paragraph). Guo et al teach that the fused cells induce protective immunity and may be a useful strategy for cancer immunotherapy (page 520, column 1, last sentence).

Van der Bruggen et al teach transfection of antigen presenting cells with nucleic acid capable of expressing a polypeptide tumor antigen (especially page 20 at lines 17-21).

Hogan et al teach antigen presenting cells that are PBL, i.e., peripheral blood lymphocytes which include activated B cells, that are peptide pulsed, i.e., cocultured with peptide antigen.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, and it was well within the purvue of the skilled artisan, to have used an anti-gp115 bispecific Mab to isolate the gp115 tumor protein of the human liver tumor cells of Shi et al, to have determined the sequence of said protein and the areas of said protein that contain peptide epitopes. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the B cells of Guo modified with a nucleic acid minigene construct of Van der Bruggen et al encoding the gp115 tumor antigen of Shi et al, or to have used the B cells of Guo pulsed with peptides from the gp115 tumor antigen of Shi et al, or to have fused the tumor cells of Shi et al with the activated B cell of Guo et al, and to have used any one of the aforementioned modified cells in the composition of Shi et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to provide a more efficient antigen presenting cell for cancer immunotherapy, to eliminate the need for cytokine pretreatment of the

tumor cells of Shi et al, and to eliminate the need for irradiation inactivation of the said tumor cells of Shi et al for in vivo immunotherapy (i.e., in order to prevent the tumor cells from proliferating the patient).

13. Claims 5 and 12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 5,484,596 in view of Renner et al (Science, Vol. 264, page 833, 1994) or Bohlen (Blood, vol. 82, pages 1803-1812, 1993), both in view of admissions in the specification, Darlington et al (JNCL, Vol. 64, page 809, 1980), Chapoval et al (J. Immunol., Vol. 155, pages 1296-1303, 1995), Krummel et al (J Exp. Med., Vol. 182, pages 459-465, 1995), Wang et al (Int. J. Cancer, Vol. 51, pages 962-967) and Vanky et al (Semin. Cancer Biol., Vol. 2(1), pages 55-62, 1991).

U.S. Patent No. 5,484,596 discloses using irradiated tumor cells as a vaccine, (especially Abstract).

U.S. Patent No. 5,484,596 does not disclose bispecific antibodies that bind to CD28 and to a tumor-associated antigen like gp55 and it does not provide motivation for bridging tumor cells to CTL via CD28.

Renner et al teach bispecific monoclonal antibodies that bind to CD28 and to tumor-associated antigens (CD30) in order to "target human T cells to the tumor cells in vivo." The exact identity of the antibody that binds to the target cell (for the elected species gp55) does not appear to be critical to the invention, see page 10, lines 25-27 of the instant specification. Assuming *arguendo* that use of antibodies recognizing gp55 from HEPA 1-6 is a critical feature of the invention, pages 22 at line 31 and page 23 at line 32 of the specification admits that HEPA 1-6 cells were known in the prior art. Darlington et al also teach such hepatoma cells. The specification admits that methods of making monoclonal antibodies were known and that methods of making bispecific antibodies were known.

Bohlen et al teach targeting of T cells to tumor cells using bispecific antibodies comprising a ligand for CD28 (especially Abstract) and page 1810 indicates that optimal responses may be maintained by the administration of CD28 antibodies to ensure proliferation and stimulation of tumor-specific T cells.

Chapoval et al teach that bispecific antibodies that bridge T cells and tumor cells trigger activation of T cells and retarget such activated T cells to tumor cells resulting in lysis of tumor cells (especially Abstract and pages 1301-1302).

Krummel et al teach that CD28 is the "major costimulatory molecule for proliferation of T cells" and that antibody engagement of CD28 on T cells augments T cell responses and can supply costimulation to T cells encountering APCs deficient in costimulation (HEPA 1-6 cells are deficient in antigen presentation because they lack MHC class I expression, see pages 29-30 of the instant specification).

Wang et al teach cytokine-induced elevation of MHC class I and ICAM-1 (CD54) expression on tumor cells treated ex vivo with TNF-α and IFN-γ (page 962, second column). Such induction is taught to result in tumor cells that interact more readily with autologous lymphocytes and induce CTL that even lyse untreated tumor cells.

Vanky et al teach that in vitro treatment of tumor cells with TNF-α and IFN-γ induces expression of MHC class I antigens and ICAM-1 and that expression of class I antigens is necessary for recognition of the tumor cells by autologous lymphocytes that lyse the tumor cells.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have armed tumor cells of U.S. Patent No. 5,484,596 with a bispecific antibody comprising a portion specific for a tumor antigen on the surface of said tumor cells and further comprising a portion specific for CD28 such as the bispecific antibodies of Renner et al, Bohlen et al and Chapoval et al, to be administered in vivo, given the teaching of Renner et al, Bohlen et al and Chapoval et al that bispecific antibodies are effective for bridging T cells and tumor cells and for inducing T cell responses to tumor cells, and it would have been prima facie obvious to have additionally treated tumor cells (including in the case of a weakly immunogenic tumor) with the TNF-α or IFN-γ cytokines to induce CTLs that even lyse untreated tumor cells.

One of ordinary skill in the art would have been motivated to do this in order to induce and/or increase an in vivo response of the cellular arm of the immune system, i.e., of CTL that would be capable of destroying tumor cells. Claim 5 is included in the instant rejection because it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have collected a pharmaceutically effective amount of the composition in order to effectively treat a tumor.

14. Claims 13-16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 5,484,596 in view of Renner et al (Science, Vol. 264, page 833, 1994) or Bohlen (Blood, vol. 82, pages 1803-1812, 1993), both in view of admissions in the specification, Darlington et al (JNCL, Vol. 64, page 809, 1980), Chapoval et al (J. Immunol., Vol. 155, pages 1296-1303, 1995), Krummel et al (J Exp. Med., Vol. 182, pages 459-465, 1995), Wang et al (Int. J. Cancer, Vol. 51, pages 962-967) and Vanky et al (Semin. Cancer Biol., Vol. 2(1), pages 55-62, 1991) as applied to claims 5 and 12 above, and further in view of Guo et al (Science, Volume 263, 1994, pages 518-520) and further in view of Van der Bruggen et al (WO 96/21673) and Hogan et al (J. Exp. Med., Volume 168, 1988, pages 725-736).

The combined references used to reject claims 5 and 12 above do not teach an immunogenic composition wherein the antigen presenting cell is a B cell, nor wherein said B cell is pulsed with peptide antigens of diseased cells or is transfected with a nucleic acid capable of expressing one or more antigens of diseased cells or their precursors, nor wherein said antigen presenting cell is fused with a diseased cell from a patient mammal.

Guo et al teach that activated B cells are the most effective antigen presenting cells (page 518, column 1, second paragraph). Guo et al further teach an antigen presenting cell that is a fusion of a tumor cell with an activated B cell (page 518, column 1, second paragraph). Guo et al teach that the fused cells induce protective immunity and may be a useful strategy for cancer immunotherapy (page 520, column 1, last sentence).

Van der Bruggen et al teach transfection of antigen presenting cells with nucleic acid capable of expressing a polypeptide tumor antigen (especially page 20 at lines 17-21).

Hogan et al teach antigen presenting cells that are PBL, i.e., peripheral blood lymphocytes which include activated B cells, that are peptide pulsed, i.e., cocultured with peptide antigen.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the B cells of Guo modified with a nucleic acid minigene construct of Van der Bruggen et al encoding a tumor antigen or the B cells of Guo pulsed with peptides from the said tumor antigen or to have fused the said tumor cells with the activated B cell of Guo et al and to have used any one of the aforementioned modified cells in the composition of the combined references.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to provide a more efficient antigen presenting cell for cancer immunotherapy and to eliminate the need for irradiation inactivation of the said tumor cells of Shi et al for in vivo immunotherapy, i.e., in order to prevent the tumor cells from proliferating the patient.

15. Claims 5 and 12-16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Guo et al (Nature Medicine, Volume 3(4), April 1997, pages 451-455) in view of Guo et al (Science, Volume 263, 1994, pages 518-520) and further in view of Van der Bruggen et al (WO 96/21673) and Hogan et al (J. Exp. Med., Volume 168, 1988, pages 725-736).

Guo et al (Nature Medicine) teach a method of preparation of a composition comprising hepa 1-6 tumor cells or EL-4 tumor cells armed with one of three bispecific monoclonal antibodies: CD28:gp55, CD28:gp95 or CD28:gp210 (especially page 451, column 2, Abstract and page 452, column 1). Guo et al further teach that said composition induces protective immunity when administered to mice (especially page 452, column 1). Guo et al teach that said tumor cells express very low levels of molecules necessary for antigen presentation and for adhesion (especially page 451, middle of column 2) and that cytokine treatment of said cells can enhance levels of said molecules (especially page 451 Abstract).

Guo et al (Science) teach that activated B cells are the most effective antigen presenting cells (page 518, column 1, second paragraph). Guo et al further teach an antigen presenting cell that is a fusion of a tumor cell with an activated B cell (page 518, column 1, second paragraph). Guo et al teach that the fused cells induce protective immunity and may be a useful strategy for cancer immunotherapy (page 520, column 1, last sentence).

Van der Bruggen et al teach transfection of antigen presenting cells with nucleic acid capable of expressing a polypeptide tumor antigen (especially page 20 at lines 17-21).

Hogan et al teach antigen presenting cells that are PBL, i.e., peripheral blood lymphocytes which include activated B cells, that are peptide pulsed, i.e., cocultured with peptide antigen.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, and it was well within the purvue of the skilled artisan, to have used an anti-gp55 bispecific Mab to isolate the gp55 tumor protein of the human liver tumor cells of Shi et al, to have determined the sequence of said protein

and the areas of said protein that contain peptide epitopes. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the B cells of Guo modified with a nucleic acid minigene construct of Van der Bruggen et al encoding the gp55 tumor antigen of Shi et al, or to have used the B cells of Guo pulsed with peptides from the gp55 tumor antigen of Shi et al, or to have fused the tumor cells of Shi et al with the activated B cell of Guo et al, and to have used any one of the aforementioned modified cells in the composition of Guo et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to provide a more efficient antigen presenting cell for cancer immunotherapy and to eliminate the need for irradiation inactivation of the said tumor cells of Guo et al for in vivo immunotherapy, i.e., in order to prevent the tumor cells from proliferating the patient.

Claim 5 is included in the instant rejection because hepa 1-6 tumor cells are weakly immunogenic, as taught by Guo et al (Nature Medicine) above, and claim 5 is included because a pharmaceutically effective amount of the composition is collected when said composition induces protective immunity when administered to mice.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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